Association Between Insulin Resistance and Bone Mass in Men

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Context: The association between insulin resistance and bone mass is still not clear.

Objective: The purpose of this study was to evaluate the association between insulin resistance and bone mass.

Design and Setting: This was a cross-sectional survey of the nationally representative population.

Participants: A total of 3113 men (aged ≥20 years) from the fourth Korean National Health and Nutrition Examination Survey of 2008–2009 were included.

Main Outcome Measures: Bone mineral density (BMD) was measured using dual-energy x-ray absorptiometry. Osteopenia and osteoporosis were defined using the World Health Organization T score criteria. Fasting plasma insulin and glucose levels were measured, and insulin resistance was evaluated using the homeostasis model assessment–estimated insulin resistance (HOMA-IR) index.

Results: Age-, height-, and weight-adjusted mean BMD values significantly decreased as quartiles of HOMA-IR and the fasting plasma insulin level increased (*P* for trends <.001). In multivariable logistic regression analyses, participants who had a higher HOMA-IR or fasting plasma insulin level had a higher odds ratio for osteoporosis/osteopenia. Interestingly, the association between fasting plasma insulin level and whole-body BMD differed by the degree of insulin resistance. In the lowest quartile of HOMA-IR, the fasting insulin level was positively associated with BMD. As insulin resistance increased, however, the fasting insulin level was inversely associated with BMD, and this relationship became more significant as the degree of insulin resistance increased.

Conclusions: In a nationally representative sample of Korean men, insulin resistance and the fasting plasma insulin level were inversely associated with bone mass. Further studies are required to confirm this association and reveal the underlying mechanisms. **(*J Clin Endocrinol Metab* 99: 988–995, 2014)**

Insulin resistance is defined as decreased cellular response to the hormonal action of insulin due to defects in the insulin signaling pathway (1). Insulin resistance has been assigned a central place in the metabolic disturbances associated with obesity and type 2 diabetes (2) and is recognized as a key component in the pathophysiology of the metabolic syndrome (3). In an insulin-resistant state, the plasma insulin level increases to compensate for the reduced responsiveness of target cells to insulin action. Because insulin is an anabolic agent for bone formation (4, 5), insulin resistance with compensating hyperinsulinemia has been shown to result in increased bone mass (6–8).

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Abbreviations: BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry; HOMA-IR, homeostasis model assessment–estimated of insulin resistance; MET, metabolic equivalent.

Furthermore, hyperinsulinemia may also have a negative impact on sex hormone–binding globulin, hence increasing free sex hormone levels, which may protect against bone loss (9, 10). On the basis of these findings and hypotheses, insulin resistance has been regarded as a protective factor for bone health. Consistent with this understanding, patients with type 2 diabetes are often shown to have increased bone mass (11–15), and this has been partly explained by the insulin resistance seen in these patients (8, 14, 16).

Nevertheless, the association between insulin resistance and bone mass remains unclear; some studies have failed to find an independent association (9, 17, 18), and an inverse association also has been reported by a few small studies (19–21). Moreover, recent studies have reported obesity to have a detrimental effect on bone mass (22, 23), which contradicts the prevailing opinion that insulin resistance is protective for bone mass. Considering that bone is receiving growing attention as a metabolically active organ which is affected by metabolic disorders, such as diabetes and obesity, the association between insulin resistance and bone needs to be further elucidated. Therefore, we aimed to evaluate this association using data from the fourth Korean National Health and Nutrition Examination Survey 2008–2009 (KNHANES IV). In the present study, we focused on general male subjects to exclude the potential effects of hormonal changes according to menstrual status in women.

Materials and Methods

Subjects

The KNHANES IV (2008–2009) was a nationwide survey representing the noninstitutionalized civilian population of South Korea. It included comprehensive information on the health and sociodemographics of 9213 men (45.4% of total participants). A complex, stratified, multistage probability sampling design was used, and sampling units were based on geographical area, age, and sex. Each sampled participant is assigned a numerical sample weight that measures the number of people in the population represented by that specific participant. A complex sampling design and sample weights make it possible to produce nationally representative data. The response rates were 77.8% and 79.2% in 2008 and 2009, respectively. Details of the KNHANES IV were described elsewhere (24). All subjects provided informed consent before inclusion in the study.

KNHANES IV included a large-scale whole-body dual-energy x-ray absorptiometry (DXA) survey, in which bone mineral density (BMD) was measured in 4486 adult men (age ≥20 years) from all 16 administrative districts of Korea. Among them, 3207 participants who had received laboratory examinations of fasting plasma glucose and insulin concentrations (fasting time ≥12 hours) were included as the initial candidates for the present study. From this population, we first excluded 18 participants who were taking prescription medications for osteoporosis (eg, bisphosphonate or hormonal agents) to control for the increase in BMD probably caused by the medications. In addition, we excluded 76 subjects who answered to the questionnaire that they had been diagnosed and treated by physician for the conditions affecting bone metabolism, such as chronic renal failure, liver cirrhosis, thyroid diseases, rheumatoid arthritis, and all types of cancer. After these exclusions, 3113 subjects were finally included in the present analysis. A flow diagram of inclusions and exclusions of study participants is shown in Supplemental Figure 1 (published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org).

Associated factors

The demographic and behavioral variables were age, equivalized monthly household income (quartiles), smoking (never smoker, past smoker, or current smoker), alcohol consumption (grams of alcohol per day), and physical activity (low, moderate, or high). The equivalized household income was calculated as the total monthly household income divided by the square root of the total number of household members. Average alcoholic beverage consumption was assessed by self-reported questionnaire and then converted into the amount of pure alcohol (in grams) consumed per day. Physical activity was quantified as the metabolic equivalent (MET) of task minutes per week, which was calculated using the scoring protocol of the Korean version of the International Physical Activity Questionnaire short form. Accordingly, physical activity levels were then classified as low (<600 MET-minutes per week), moderate (≥600–<3000 MET-minutes per week), or high (≥3000 MET-minutes per week). The 24-hour recall method was used to assess calcium intake (milligrams per day). Anthropometric factors, such as body weight and height, were obtained using standard protocols and were measured to the nearest 0.1 kg and 0.1 cm, respectively.

Laboratory examinations

During the survey, antecubital vein blood samples were drawn and immediately centrifuged. Plasma total cholesterol (milligrams per deciliter), high-density lipoprotein (HDL) cholesterol (milligrams per deciliter), low-density lipoprotein (LDL) cholesterol (milligrams per deciliter), triglyceride (milligrams per deciliter), fasting glucose (milligrams per deciliter), and fasting insulin concentrations (micro-International units per milliliter) were measured enzymatically using a Hitachi automatic analyzer 7600. Insulin resistance was evaluated using the homeostasis model assessment–estimated insulin resistance (HOMA-IR) index (ie, HOMA-IR = [fasting plasma glucose] × [fasting plasma insulin]/405) (25). Serum vitamin D concentration (nanograms per milliliter) was measured by RIA (DiaSorin Inc) using a γ-counter (1470 Wizard; PerkinElmer).

DXA measurements and definition of osteopenia/osteoporosis

All participants included in our study had undergone DXA (DISCOVERY-W fan-beam densitometer; Hologic Inc) for assessment of BMD (grams per square centimeter) of the whole body, femoral neck, and lumbar spine (L1–L4), as well as body composition, including percent fat mass (total fat mass/total mass ×100, percentage). Well-trained and qualified technicians performed standardized daily quality control of DXA instruments using spine phantom; accurate and reliable data were generated, which were then analyzed using

industry standard techniques at the Korean Society of Osteoporosis using Hologic Discovery software (version 13.1) in its default configuration. The diagnosis of osteopenia or osteoporosis was made using World Health Organization T score criteria ($-2.5 <$ T score < -1 and T score ≤ -2.5, respectively), and the maximum BMD value for Japanese patients was used as a reference owing to the lack of established diagnostic criteria for Korean patients (26). If a participant had a low T score from one of the BMD measurements of the lumbar spine or femoral neck or both, the participant was classified as having osteopenia or osteoporosis.

Statistical analysis

The participants' characteristics were compared according to the quartiles of HOMA-IR and fasting plasma insulin concentration and are presented as means ± SE or as a proportion (percentage). Least square means of BMD, adjusted for age, weight, and height, were compared across the quartiles of HOMA-IR and fasting plasma insulin concentration, and a multiple linear regression analysis was used to test for a linear trend. We performed multivariate regression analysis to evaluate the relationship between BMD and logarithm-transformed indicators of insulin resistance, such as HOMA-IR and fasting plasma insulin concentration. In model 1, we adjusted for several continuous variables, such as age, weight, height, alcohol consumption, daily calcium intake, and serum vitamin D concentration, as well as categorical variables, such as income, smoking status, physical activity, and diabetes mellitus. Model 2 was also adjusted for percent fat mass. Finally, model 3 was further adjusted for lipid profile, including plasma total cholesterol, HDL cho-

Table 1. Characterization of Participants According to Quartiles of HOMA-IR and Plasma Fasting Insulin

	HOMA-IR[a]				Plasma Fasting Insulin[b]			
	Quartile 1 (<151)	Quartile 2 (1.51–1.96)	Quartile 3 (1.96–2.63)	Quartile 4 (≥2.63)	Quartile 1 (<6.54 μIU/mL)	Quartile 2 (6.54–8.40 μIU/mL)	Quartile 3 (8.40–10.82 μIU/mL)	Quartile 4 (≥10.82 μIU/mL)
Age, y	51.3 ± 0.6	48.3 ± 0.6	48.9 ± 0.6	50.3 ± 0.6	52.9 ± 0.6	49.8 ± 0.6	47.8 ± 0.6	48.1 ± 0.6
Weight, kg	62.7 ± 0.3	67.5 ± 0.3	70.8 ± 0.3	74.2 ± 0.4	62.6 ± 0.3	67.8 ± 0.3	70.4 ± 0.3	74.9 ± 0.4
Height, cm	168.5 ± 0.2	169.7 ± 0.2	169.5 ± 0.2	169.7 ± 0.2	168.2 ± 0.2	169.4 ± 0.2	169.9 ± 0.2	170.0 ± 0.2
Body mass index, kg/m^2	22.1 ± 0.1	23.4 ± 0.1	24.6 ± 0.1	25.7 ± 0.1	22.1 ± 0.1	23.6 ± 0.1	24.4 ± 0.1	25.9 ± 0.1
Fat mass, %[c]	18.2 ± 0.2	20.7 ± 0.2	22.6 ± 0.2	24.1 ± 0.2	18.4 ± 0.2	20.8 ± 0.2	22.4 ± 0.2	24.2 ± 0.2
Household income, %[d]								
Quartile 1 (low)	23.5	19.3	16.1	17.2	23.1	21.4	16.6	14.8
Quartile 2	26.1	22.8	23.5	24.0	26.9	22.3	23.5	23.6
Quartile 3	25.2	28.8	31.1	30.2	25.5	27.8	31.9	30.4
Quartile 4 (high)	25.3	29.1	29.3	28.6	24.5	28.5	28.1	31.3
Physical activity, %[e]								
Low	18.6	22.6	20.5	27.6	18.6	20.5	22.5	27.9
Moderate	37.5	37.8	42.0	43.0	37.6	36.3	42.7	44.0
High	44.0	39.6	37.6	29.4	43.8	43.2	34.8	28.1
Smoker, %								
Never	17.7	20.2	21.9	19.1	16.5	21.9	20.0	20.6
Past	33.5	36.3	39.3	41.1	36.0	36.9	38.3	39.1
Current	48.8	43.5	38.8	39.8	47.6	41.2	41.7	40.3
Alcohol, g/d	15.1 ± 0.7	13.4 ± 0.6	13.3 ± 0.6	12.9 ± 0.6	15.8 ± 0.7	14.0 ± 0.6	12.3 ± 0.6	12.4 ± 0.6
Calcium intake, mg/d	528.0 ± 13.5	532.9 ± 13.2	550.2 ± 13.2	533.7 ± 13.6	529.5 ± 13.9	543.9 ± 13.0	528.3 ± 13.3	542.2 ± 13.4
Serum vitamin D, ng/mL	22.2 ± 0.3	21.0 ± 0.3	21.0 ± 0.3	20.4 ± 0.2	22.4 ± 0.3	21.2 ± 0.3	20.7 ± 0.3	20.3 ± 0.2
Fasting insulin, μIU/mL[b]	5.5 ± 0.0	7.6 ± 0.0	9.4 ± 0.1	14.2 ± 0.2	5.4 ± 0.0	7.5 ± 0.0	9.5 ± 0.0	14.8 ± 0.2
Fasting glucose, mg/dL[b]	89.0 ± 0.3	94.1 ± 0.4	99.4 ± 0.6	113.7 ± 1.2	94.8 ± 0.8	99.6 ± 0.9	98.8 ± 0.7	103.6 ± 0.8
HOMA-IR	1.2 ± 0.0	1.7 ± 0.0	2.2 ± 0.0	3.8 ± 0.0	1.3 ± 0.0	1.8 ± 0.0	2.3 ± 0.0	3.8 ± 0.1
Total cholesterol, mg/dL	182.7 ± 1.2	187.2 ± 1.3	187.8 ± 1.3	190.3 ± 1.4	184.0 ± 1.2	188.1 ± 1.2	186.4 ± 1.3	189.5 ± 1.3
HDL cholesterol, mg/dL	53.4 ± 0.5	50.6 ± 0.4	47.3 ± 0.4	45.5 ± 0.4	53.4 ± 0.5	50.3 ± 0.4	47.0 ± 0.4	45.7 ± 0.4
LDL cholesterol, mg/dL	106.2 ± 1.1	108.2 ± 1.3	107.9 ± 1.1	105.6 ± 1.4	106.0 ± 1.2	109.3 ± 1.2	106.5 ± 1.2	106.0 ± 1.3
Triglycerides, mg/dL	115.7 ± 3.0	141.7 ± 4.5	162.8 ± 3.8	196.0 ± 5.2	123.0 ± 3.6	142.6 ± 4.0	164.6 ± 4.4	189.0 ± 5.0

Data represent means ± SE or prevalence (%).

[a] HOMA-IR = (fasting plasma glucose) × (fasting plasma insulin)/405.

[b] Fasting time ≥12 hours.

[c] Percent fat mass = total fat mass/total mass × 100.

[d] Monthly equivalized household income.

[e] Defined as low (<600 MET-minutes per week), moderate (≥600–<3000 MET-minutes per week), and high (≥3000 MET-minutes per week) levels of physical activity.

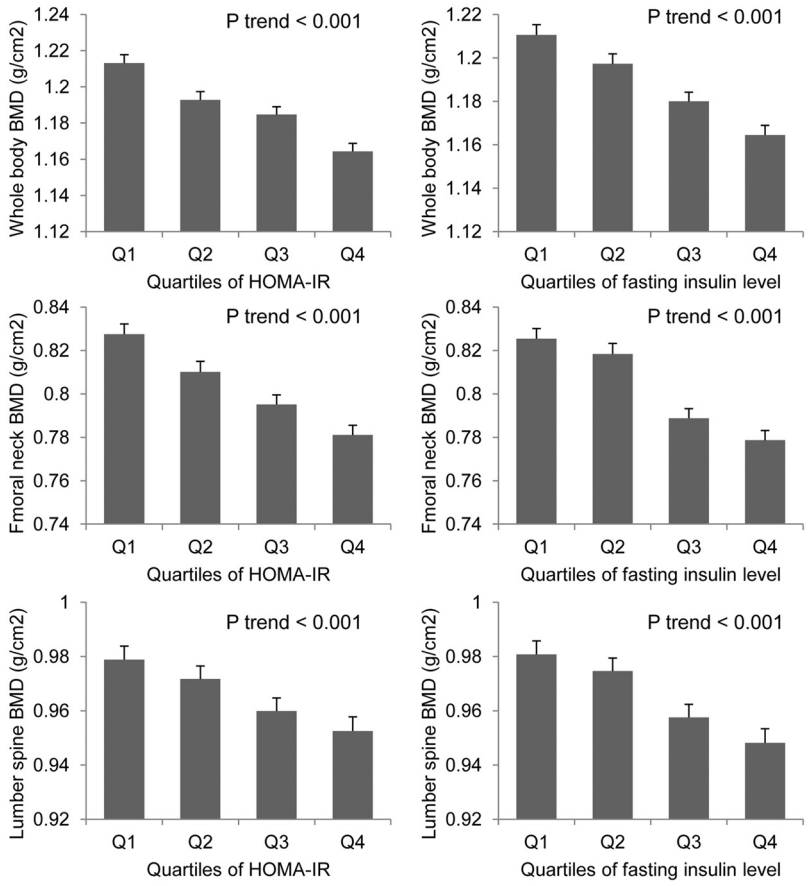

Figure 1. Association between insulin resistance or fasting plasma insulin levels and BMD. Age-, weight-, and height-adjusted least-square means (SE) of whole-body, femoral neck, and lumbar spine BMD across quartiles of HOMA-IR and fasting plasma insulin concentration are shown. The bars from left to right are quartiles 1, 2, 3, and 4 of HOMA-IR and fasting plasma insulin concentration.

lesterol, and triglyceride concentrations. Because there was significant collinearity between LDL and total cholesterol levels, LDL cholesterol was not included as a covariate in model 3. We also performed multivariable logistic regression analysis to estimate adjusted odds ratios and 95% confidence intervals for osteopenia/osteoporosis across quartiles of HOMA-IR and fasting plasma insulin concentration, using the lowest quartiles as references. Finally, we evaluated the relationship between logarithm-transformed fasting plasma insulin level and whole-body BMD according to HOMA-IR quartiles using multiple linear regression analysis after adjustment for all variables in model 3. Statistical analyses were performed using STATA 12.1 (Stata Corp) with the svy command to account for the complex sampling design and included sample weights, which enabled the results to represent the entire national male adult population. Reported probability values are two-sided, and a value of $P < .05$ was considered statistically significant.

Results

Table 1 presents the characteristics of the 3113 participants (mean age, 49.7 years) across the quartiles of HOMA-IR and fasting plasma insulin concentrations. Overall, the estimated prevalence of osteopenia and osteoporosis weighted to the total population was 33.2% and 3.1%, respectively.

As shown in Figure 1, HOMA-IR and fasting plasma insulin levels were inversely related to BMD. Age-, height-, and weight-adjusted BMD means of the whole body, femoral neck, and lumbar spine significantly decreased as quartiles of HOMA-IR and fasting plasma insulin levels increased (P for trends $<.001$).

In Table 2, BMDs of the whole body, femoral neck, and lumbar spine were inversely associated with logarithm-

Table 2. Multivariate-Adjusted Association Between Indicators of Insulin Resistance and BMD

	Whole-Body BMD		Femoral Neck BMD		Lumbar Spine BMD	
	$\beta \pm$ SE	*P* Value	$\beta \pm$ SE	*P* Value	$\beta \pm$ SE	*P* Value
LN (HOMA-IR)[a]						
Model 1[b]	−0.041 ± 0.006	<.001	−0.037 ± 0.006	<.001	−0.023 ± 0.007	.001
Model 2[c]	−0.027 ± 0.006	<.001	−0.024 ± 0.006	<.001	−0.015 ± 0.007	.042
Model 3[d]	−0.025 ± 0.007	.001	−0.021 ± 0.006	.001	−0.013 ± 0.007	.070
LN (fasting insulin)[a]						
Model 1[b]	−0.050 ± 0.007	<.001	−0.046 ± 0.007	<.001	−0.031 ± 0.008	<.001
Model 2[c]	−0.034 ± 0.007	<.001	−0.031 ± 0.007	<.001	−0.022 ± 0.008	.007
Model 3[d]	−0.032 ± 0.007	<.001	−0.028 ± 0.007	<.001	−0.021 ± 0.008	.012

[a] Values were transformed to natural logarithmic scale.

[b] Model 1: adjusted for age, weight, height, smoking status, alcohol consumption, income, physical activity, calcium intake, serum vitamin D concentration, and diabetes.

[c] Model 2: adjusted for percent fat mass in addition to model 1.

[d] Model 3: adjusted for plasma total cholesterol, HDL cholesterol, and triglyceride concentrations in addition to model 2.

Table 3. Odds Ratios for Osteopenia/Osteoporosis According to Quartiles of HOMA-IR or Plasma Fasting Insulin Level

			aOR (95% CI)		
	Median (range)	**Proportion, %[c]**	**Model 1[d]**	**Model 2[e]**	**Model 3[f]**
HOMA-IR[a]					
Quartile 1	1.24 (<1.51)	38.6	1.00 (reference)	1.00 (reference)	1.00 (reference)
Quartile 2	1.75 (1.51–1.96)	32.1	1.21 (0.90–1.62)	1.14 (0.85–1.55)	1.12 (0.83–1.52)
Quartile 3	2.25 (1.96–2.63)	28.5	1.57 (1.16–2.11)	1.33 (0.98–1.81)	1.27 (0.93–1.74)
Quartile 4	3.37 (≥2.63)	33.1	1.90 (1.38–2.61)	1.59 (1.15–2.21)	1.49 (1.07–2.08)
P for trend	—	—	<.001	.004	.015
Plasma fasting insulin level[b]					
Quartile 1	5.57 (<6.54)	40.1	1.00 (reference)	1.00 (reference)	1.00 (reference)
Quartile 2	7.48 (6.54–8.40)	29.7	1.08 (0.81–1.45)	1.01 (0.75–1.37)	1.00 (0.74–1.36)
Quartile 3	9.42 (8.40–10.82)	32.6	1.69 (1.26–2.28)	1.46 (1.08–1.99)	1.41 (1.04–1.92)
Quartile 4	13.35 (≥10.82)	30.1	1.82 (1.32–2.51)	1.50 (1.02–2.09)	1.42 (1.02–2.00)
P for trend			<.001	.003	.009

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval.

[a] HOMA-IR = (fasting plasma glucose) × (fasting plasma insulin)/405.

[b] Fasting time ≥12 hours.

[c] Weighted proportion of participants with osteopenia/osteoporosis.

[d] Model 1: adjusted for age, weight, height, smoking status, alcohol consumption, income, physical activity, calcium intake, serum vitamin D concentration, and diabetes.

[e] Model 2: adjusted for percent fat mass in addition to model 1.

[f] Model 3: adjusted for plasma total cholesterol, HDL cholesterol, and triglyceride concentrations in addition to model 2.

transformed HOMA-IR and fasting plasma insulin concentration after adjustment for various confounders in model 1. Compared with model 1, β coefficients decreased somewhat in model 2 in which percent fat mass was also adjusted for. However, all inverse associations were still significant. Compared with results for model 2, further adjustment for the lipid profile in model 3 did not significantly alter the results, except for the association between HOMA-IR and lumbar spine BMD, which became marginally significant ($P = .070$). In addition, there was no meaningful relationship between BMD and logarithm-transformed fasting plasma glucose concentration (data not shown).

In multivariable logistic regression analyses, inverse associations between indicators of insulin resistance (HOMA-IR and fasting plasma insulin level) and bone health were found (Table 3). In all models, there were significant increasing trends of odds ratios for osteopenia/osteoporosis as quartiles of HOMA-IR and fasting plasma insulin level increased. Furthermore, subjects in the highest quartiles of HOMA-IR and fasting plasma insulin concentration had 49% and 42% higher odds of having osteopenia/osteoporosis, respectively, compared with those in the lowest quartiles after adjustment for various potential confounders in model 3. In contrast, there was no such association between fasting plasma glucose levels and BMD or bone health (data not shown).

To examine whether the association between fasting plasma insulin level and BMD differed by the degree of insulin resistance, we performed multiple regression analysis between fasting plasma insulin level and whole-body BMD according to HOMA-IR quartiles (Figure 2). After adjustment for all variables in model 3, a significant positive relationship between fasting plasma insulin level and whole-body BMD was found in the lowest quartile of HOMA-IR (quartile 1; $\beta = 0.073$, $P = .017$). However, direction of the association became negative in higher HOMA-IR quartiles (quartiles 2, 3, and 4), and the associations became more significant as the quartiles increased. Therefore, the relationship between fasting plasma insulin level and bone mass seemed to be affected by the degree of insulin resistance.

In addition, the results did not change significantly when diabetic patients were excluded rather than adjusted as a covariate (n = 2896; data not shown).

Discussion

In our study, HOMA-IR and fasting plasma insulin concentration were inversely associated with BMD and osteopenia/osteoporosis in a sample of Korean men who were representative of the general national population. These results suggest that insulin resistance is a negative predictor for bone health. Furthermore, the association between plasma fasting insulin level and BMD differed according to the degree of insulin resistance.

Hyperinsulinemia has been reported to be associated with increased bone mass (6–8, 27, 28) owing to the an-

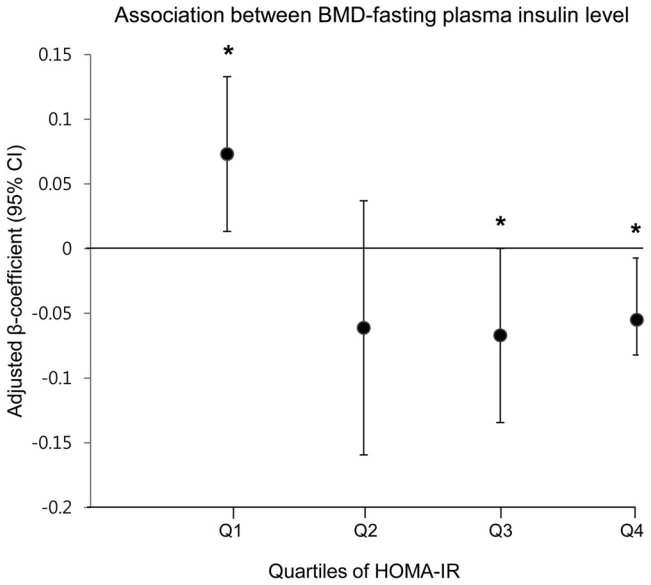

Figure 2. Association between fasting plasma insulin level and BMD according to the degree of insulin resistance. Whole-body BMD and logarithm-transformed fasting plasma insulin levels were used. Adjusted β coefficients and 95% confidence intervals (CIs) were calculated using multiple linear regression analysis after adjustment for age, weight, height, smoking status, alcohol consumption, income, physical activity, calcium intake, serum vitamin D concentration, diabetes, percent fat mass, plasma total cholesterol, HDL cholesterol, and triglyceride concentrations and compared according to quartiles of HOMA-IR. *, $P < .05$.

abolic effect of insulin (4, 5) and increases in free sex hormone levels (9). Because hyperinsulinemia is both a result and a driver of insulin resistance (2), insulin resistance has also been found to be associated with increased bone mass (7, 9). This positive association between insulin resistance and bone mass has been used to explain the higher BMD seen in patients with type 2 diabetes (8, 14, 16) and obese subjects (29). Interestingly, however, the present study showed inverse relationships between insulin resistance or fasting plasma insulin level and bone mass, and thus contradicted the above findings and suggestions. Instead, ours was consistent with a few recent small studies conducted with specific population, such as adolescents (19), subjects who previously received bone marrow transplants (21), and patients with type 2 diabetes (20). Furthermore, our results were also compatible with recent findings that have shown reduced BMD to be associated with conditions related to insulin resistance, such as metabolic syndrome (30) and increased fat mass (22, 23). One reason for the difference between the results of previous studies and ours is whether potential confounding factors are sufficiently controlled or not. Some previous studies that reported opposite results did not consider the confounders that could mediate between insulin resistance and bone mass (7, 27). Furthermore, other studies found that positive relationships between hyperinsulinemia or insulin resistance and bone mass were attenuated and became nonsignificant after adjustment for body weight or BMI (9, 28). It seems reasonable because an increase in body weight or BMI, commonly seen in insulin-resistant subjects, is a strong protective factor for bone mass (31). Therefore, controlling for various confounding factors, including weight or BMI, is necessary in the assessment of the association between insulin resistance and bone mass. In contrast to the previous studies, we controlled for numerous potential confounders including weight, percent fat mass, lipid profile, and other demographic factors in the present study. Moreover, our study is unique in that we studied a nationally representative, large population.

Possible explanations for the inverse relationship between insulin resistance and bone health include both indirect and direct mechanisms. Indirect mechanisms could be mediated by several factors. First, levels of proinflammatory cytokines, such as IL-6 and TNF-α, are increased in insulin-resistant subjects and may induce bone loss by stimulating osteoclast activity (32, 33). Because KNHANES IV does not include data on such parameters, we could not assess this possibility in the present study; further studies are needed to examine this aspect. Second, increases in fat mass in subjects with insulin resistance could also influence BMD, because fat mass is known to affect bone as a major weight-bearing component and as a metabolically active organ (22, 23). To evaluate whether fat mass has a role in the association between insulin resistance and BMD, we compared the results obtained before and after adjustment for percent fat mass (model 1 vs model 2). Compared with model 1, the association between insulin resistance and bone health was somewhat attenuated in model 2, although the results remained significant. Therefore, increases in fat mass in insulin-resistant subjects could not fully explain the inverse association between insulin resistance and bone health. Third, altered lipid profiles in insulin-resistant subjects may also affect bone health, considering that levels of various blood lipids have been shown to be associated with BMD (34, 35). In our study, however, the inverse association between insulin resistance and BMD was not greatly changed after further adjustment for plasma total cholesterol, HDL cholesterol, and triglyceride levels (model 3).

Along with the possible indirect mechanisms described above, insulin resistance may also directly affect bone mass. Bone is now recognized as an insulin target organ (36, 37), and insulin receptor signaling in osteoblasts has been found to be important for proliferation, differentiation, and survival of osteoblasts (37, 38). Interestingly, a recent animal study showed that insulin resistance induced by a high-fat diet impaired osteoblastic insulin signaling, which led to decreased proliferation and survival of os-

teoblasts and resulted in osteoporosis in the jawbone of rats (39). Another study also reported that insulin-dependent functions in osteoblasts were disrupted in high-fat diet–fed mice, and insulin resistance in osteoblasts contributes to the development of systematic insulin resistance in mice (40). On the basis of these studies, it is hypothesized that bone may be another site of insulin resistance, and interruption of osteoblastic insulin signaling in insulin-resistant subjects could directly result in a reduction of bone mass. Although we could not further investigate this hypothesis, future studies should be focused on this issue by measuring not only biochemical markers of bone formation and resorption but also measures of insulin signaling in osteoblasts, such as circulating levels of various forms of osteocalcin.

In contrast to the previous studies, we found that fasting hyperinsulinemia was inversely associated with BMD in subjects overall. Interestingly, however, the association between the fasting insulin level and whole-body BMD differed according to HOMA-IR quartile (Figure 2). Although the fasting plasma insulin level was a part of the HOMA-IR calculation, multicollinearity was not a problem in this analysis, because we stratified by HOMA-IR first and then performed the regression analysis in each stratum afterward. In the lowest quartile of HOMA-IR, hyperinsulinemia was significantly associated with increased bone mass, consistent with insulin being an anabolic agent for bone. However, the fasting insulin level was inversely associated with BMD in the higher quartiles of HOMA-IR, and this relationship became more significant as the degree of insulin resistance increased. This phenomenon can support both the indirect and direct mechanisms that we suggested above. First, as insulin resistance became more severe, factors associated with insulin resistance, such as inflammatory cytokines, increased and exerted more detrimental effects on bone mass, which might overcome the anabolic effect of insulin on bone and result in reduced bone mass (indirect mechanism). Second, insulin could not exert its anabolic effect on bone in subjects with insulin resistance because of impaired insulin signaling in osteoblasts (direct mechanism). The latter explanation can be applied to the suggestions of the above-mentioned animal studies (39, 40) that bone is a site of insulin resistance and interruption of osteoblastic insulin signaling may reduce bone mass. Because of the limitations of the study characteristics and measurements, however, the results of our study are not adequate to confirm the possibility of either direct or indirect mechanisms that we suggested above. Hence, further clinical and basic research studies are needed to verify our suggestions and reveal molecular mechanisms.

The present study also has other limitations. First, exact cause-and-effect relationships could not be determined owing to the cross-sectional nature of our study. Second, some evaluations regarding participants' health status were based on a self-reported questionnaire, which may be inaccurate. Third, HOMA-IR may not be an appropriate indicator of insulin resistance in particular subjects. Nevertheless, HOMA-IR has been generally well correlated with insulin resistance as assessed by other validated methods and, therefore, is regarded as a simple and reliable surrogate measure of insulin resistance in large-scale epidemiologic studies like ours (41). Despite these limitations, our study is important because it focuses on a current hot issue, deals with a nationally representative large population, contradicts previous findings, and proposes possible suggestions that have to be elucidated in the future.

In conclusion, insulin resistance and fasting hyperinsulinemia are inversely associated with bone mass in men. Either direct or indirect mechanisms can possibly explain such associations. Further longitudinal and experimental studies are required to confirm our findings and reveal the underlying mechanisms.

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